GENELABS TECHNOLOGIES, INC.

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April 19, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Initiation of Procedure to Determine Whether DHEA is Excluded from the Definition of "Dietary Supplement"

Dear Sir or Madam:

**CITIZEN PETITION**

The undersigned, on behalf of Genelabs Technologies, Inc., developer of the GL701 formulation of dehydroepiandrosterone ("DHEA") for the treatment of systemic lupus erythematosus ("SLE"), submits this petition under Section 201(ff) of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act") and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take the following series of actions:

## I. ACTIONS REQUESTED

A. Publish a notice in the *Federal Register* in the form of Attachment 1 requesting the submission from any interested person of information establishing that DHEA is **not** excluded from the definition of "dietary supplement" under Section 201(ff)(3)(B)(ii) of the FFDCA. The form of notice proposed in Attachment 1 is based on the information FDA generally requires for claiming a "grandfather" exemption from the new drug definition, 21 C.F.R. § 314.200(e)(2), and the requirements for premarket notification for new dietary ingredients, 21 C.F.R. Part 190; and

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B. Receive comments on the Federal Register notice for a period of 90 days; and

C. Depending on whether, during the comment period, FDA has received substantial and credible evidence that DHEA is not excluded from the definition of "dietary supplement" under Section 201(ff)(3)(B)(ii) of the FFDCA, either

(1) if FDA **has not** received any such evidence, publish, within 60 days of the close of the comment period, a ruling that DHEA may not be marketed as a "dietary supplement"; or

(2) if FDA **has** received such evidence, publish, within 120 days after the close of the comment period, a notice in the *Federal Register* stating FDA's determination whether DHEA is excluded from the definition of "dietary supplement" under Section 201(ff)(3)(B)(ii) of the FFDCA, and the reasons therefor.

## II. GROUNDS FOR REQUEST

For more than six years, Genelabs has been involved in investigating the safety and effectiveness of the drug DHEA for the treatment of systemic lupus erythematosus, a rare but severe chronic autoimmune disease for which current treatment is inadequate. In September 1999, Genelabs successfully completed a second pivotal Phase III clinical trial of DHEA for the treatment of SLE. Most recently, the company announced its plans to begin the submission of a "rolling" new drug application ("NDA") in the first half of this year with the complete submission expected before the end of the year. Because Genelabs hopes to receive FDA approval to market DHEA as a prescription medication

in the near future, Genelabs is understandably concerned about the continued unlawful marketing of DHEA as a dietary supplement.

To resolve the legal status of DHEA in a timely manner, Genelabs respectfully requests the prompt initiation of a public process for determining whether DHEA may legally be marketed as a "dietary supplement." Genelabs submits that the marketing of DHEA as a dietary supplement is contrary to law because, among other reasons, DHEA was not marketed as a dietary supplement or a food in the United States prior to the authorization, initiation, and public disclosure of substantial clinical trials involving DHEA.

In August 1998, Genelabs submitted substantial and credible information to FDA showing that DHEA was not marketed as a dietary supplement or a food prior to the authorization and public disclosure of substantial clinical drug trials involving DHEA. This information is discussed below and attached to this petition. Genelabs is not aware of any information that has been submitted to the Agency to date that would rebut the information submitted by Genelabs regarding the lack of prior marketing of DHEA as a food or dietary supplement. Given Genelabs' submission to FDA of substantial and credible information on this question, the burden has now shifted to those who support the continued marketing of DHEA as a dietary supplement to come forward with evidence to the contrary.

To enable the Agency to reach a timely and appropriate resolution of the legal status of DHEA, Genelabs requests that the Commissioner promptly initiate a public, transparent, and equitable process by which FDA would provide all interested persons the opportunity to submit evidence to establish with finality whether DHEA is excluded from the definition of a dietary supplement. A public process such as that outlined in this petition would enable FDA to develop the factual record necessary to reach a regulatory determination on the legal status of DHEA. In addition, such a process will provide the most objective and fair method of reaching such a decision.

## III. LEGAL BASIS FOR REQUEST

As provided in the Dietary Supplement Health and Education Act of 1994, Pub. L. No. 104-417 (the "DSHEA"), Section 201(ff)(1) of the Act defines a "dietary supplement" as a product intended to supplement the diet that bears or contains one or more of a list of specified dietary ingredients. Those ingredients are: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

Even if a product satisfies Section 201(ff)(1) of the Act, however, it may nevertheless be excluded from the definition of "dietary supplement" by Section 201(ff)(3)(B)(ii), which removes from the definition:

> an article authorized for investigation as a new drug ... for which substantial clinical studies have been instituted and for which the existence of such investigations has been made public, which was not before such ... authorization marketed as a dietary supplement or a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act.

Genelabs has previously submitted evidence to FDA demonstrating that DHEA is not included within the definition of "dietary supplement" under Section 201(ff)(1) because it is a naturally occurring hormone that is not found in any food that is known to constitute an element of American diets; it is therefore not a "dietary substance" within the meaning of the statute. Although Genelabs continues to support that position, in this petition Genelabs is not asking FDA to decide that question. Rather, in this petition, Genelabs is asking the Agency to focus only on the issue of whether DHEA -- if it were otherwise a dietary substance -- is nevertheless **excluded** from the statutory definition of

a dietary supplement pursuant to Section 201(ff)(3)(B)(ii). If FDA determines that DHEA is so excluded, it will be unnecessary for the Agency to decide whether DHEA is a dietary substance in the first place.

Genelabs asserts that DHEA falls squarely within the Section 201(ff)(3)(B)(ii) exclusion from the definition of a dietary supplement because: (1) DHEA has been authorized by FDA for clinical investigation as a new drug; (2) substantial clinical investigations of DHEA have been instituted; (3) the existence of these clinical investigations has been made public; (4) DHEA was not marketed as a dietary supplement or a food prior to the authorization of the substantial clinical trials involving DHEA (and the initiation and public disclosure of those clinical studies); and (5) FDA has not issued a regulation finding that the marketing of DHEA as a dietary supplement is lawful. (*See* Part IV below.) Moreover, the exclusion of DHEA from the definition of dietary supplement pursuant to Section 201(ff)(3)(B)(ii) is consistent with the public policy goals underlying this statutory provision, which seeks to balance the interests of health food consumers against the needs of patients. (*See* Part V below.) Genelabs urges FDA to act promptly, because of the effect FDA's decision (or absence of one) may have on the ability to make GL701, Genelabs' proprietary formulation of DHEA, available to patients with SLE if the NDA is approved by FDA in 2001. (*See* Part VI below.) Finally, Genelabs has laid out an orderly legal process by which FDA can rule on this matter. (*See* Part VII below.)

## IV. EVIDENCE SUPPORTING THE APPLICABILITY OF THE SECTION 201(ff)(3)(B)(ii) EXCLUSION TO DHEA

The following facts support Genelabs' assertion that DHEA may not be legally marketed as a "dietary supplement" even if it were otherwise a dietary substance:

A. FDA has authorized numerous clinical trials for the study of DHEA as a new drug.

FDA has authorized the clinical investigation of DHEA as a new drug pursuant to a number of investigational new drug ("IND") applications. The earliest clinical study of DHEA authorized pursuant to an IND of which Genelabs is aware was initiated by Elan Pharmaceuticals prior to or during December 1988 (Attachment 2). In addition, on December 29, 1988 FDA assigned IND number 32,554 to researchers at the University of California, San Diego ("UCSD") for the study of DHEA (Attachment 3).

In 1991, Stanford University researchers initiated a clinical program involving DHEA for the treatment of SLE pursuant to IND 37,873. The rights to the data from these Stanford University studies were licensed to Genelabs on November 11, 1993.

Genelabs first obtained IND authorization to undertake clinical studies involving DHEA as a new drug in January 1994. Genelabs filed an IND application for the study of DHEA in the treatment of SLE on December 22, 1993, which FDA accepted for filing on January 6, 1994 and assigned IND 44,258 (Attachment 4). Later that same year, on July 13, 1994, FDA issued an orphan drug product designation for DHEA for the treatment of SLE and the reduction in the use of steroids in steroid-dependent SLE patients, pursuant to 21 CFR Part 316. FDA also designated Genelabs' DHEA product for the treatment of SLE for expedited development under 21 CFR Part 312, Subpart E on June 20, 1995.

Thus, FDA authorized the study of DHEA as a drug pursuant to no fewer than four INDs between 1988 and 1994.

B. The clinical investigations of DHEA as a new drug have been substantial in size, design, and purpose.

In December 1988, Elan Pharmaceuticals publicly announced the initiation of a Phase I clinical trial of DHEA to evaluate the drug's safety and efficacy at different dose levels in HIV positive patients in the United States (Attachment 2). According to the published results, in that Phase I study 31 patients were given DHEA at escalating dose levels over a 16-week study period (Attachment 2).

Between 1990-1994, researchers at UCSD initiated a series of clinical studies to examine a number of significant issues involving DHEA (Attachment 3). Specifically, the UCSD researchers initiated clinical studies in 1990 (to determine endocrine-metabolic impacts of a pharmacological dose of 1600 mg/day DHEA for four weeks' duration in postmenopausal women), 1992 (to determine the effects of "replacement doses" of 50mg/day DHEA in age-advanced men), 1993 (to assess the biological endpoints of DHEA at 100mg per day), and 1994 (to assess the effects of DHEA 50 mg/day on the immune function in age-advanced men). These studies involved the administration of DHEA to 6 patients (1990 study), 30 patients (1992 study), 16 patients (1993 study), and 9 patients (1994 study), respectively.

Prior to the November 11, 1993, licensing agreement between Stanford University and Genelabs, Stanford researchers conducted substantial Phase I and Phase II clinical studies of DHEA for the treatment of SLE pursuant to IND 37,873. These studies included a placebo-controlled Phase II study of 28 women with SLE conducted over a three-month period during 1993, which demonstrated a clinical benefit in the DHEA-treated group in all of the efficacy variables as well as a reduction in the treated group of the mean dose of the drug prednisone (Attachment 5). Prednisone, the current standard therapy for treating patients with SLE, is associated with significant adverse effects.

On May 10, 1994, Genelabs initiated a Phase II/III clinical trial of the GL701 formulation of DHEA. This Phase II/III clinical trial was a randomized, double-blind,

placebo controlled, multicenter trial for the treatment of mild to moderate SLE in women who require prednisone or other steroids for their treatment. The Phase III trial enrolled 191 women beginning in May 1994 and was completed in January 1997; approximately 25% of the study patients had been enrolled at the time of the passage of the DSHEA in October 1994 (Attachment 6). Patients in that trial received daily doses of either 100 mg or 200 mg of GL701 or placebo for seven to nine months. Data presented to the American College of Rheumatology on behalf of the company in 1997 showed that patients who received GL701 achieved the study's primary endpoint -- the sustained reduction in their steroid dose while maintaining stable or reduced disease activity -- at a higher rate than placebo (Attachment 7).

Genelabs instituted a second pivotal Phase III trial in March 1996. That study enrolled 381 women with SLE randomized to receive either DHEA or placebo over a 12-month period. Patient enrollment was completed in March 1998. On March 31, 1999, FDA designated GL701 for "Fast Track" review (Attachment 8). On September 21, 1999, Genelabs announced positive results from this second pivotal trial (Attachment 9).

C. The clinical investigations of DHEA have been made public.

As noted, Elan Pharmaceuticals publicly disclosed the initiation of clinical trials with DHEA in December 1988 (Attachment 2). The results from the Elan Phase I study were published in the *Journal of Acquired Immune Deficiency Syndromes* 6: 459-465 (1993) (Attachment 2).

Similarly, the results of each of the four UCSD studies involving DHEA conducted between 1990-1994 were publicly disclosed and published (Attachment 3). The results of the 1990 study were presented in 1990 at the 72nd Annual Meeting of the Endocrine Society and published in the *Journal of Clinical Endocrinology & Metabolism* 71:696-704 (1990). The results of the 1992 study were presented in 1992 at the Annual

Meeting of the Endocrine Society and later published in the *Journal of Clinical Endocrinology & Metabolism* 78:1360-1367 (1994). The results of the 1993 study were published in the *Annals of the New York Academy of Sciences* 774:128-142 (1995). The results of the 1994 study were published in the *Journal of Gerontology: Medical Sciences* 52a:M1-M7 (1997).

Both the Phase II/III clinical trial conducted by Genelabs and the earlier Stanford University studies were made public through a variety of channels. For example, Genelabs publicly disclosed the existence of the Stanford University trials in a press release on November 11, 1993 (Attachment 5). Moreover, in November 1993, the results of the Stanford University studies were presented by Dr. Ronald van Vollenhoven at the Annual Meeting of the American College of Rheumatology in San Antonio, Texas, and published in *Arthritis & Rheumatism*, the peer-reviewed journal of the American College of Rheumatology, in September 1994 and December 1995 (Attachment 10). The existence and initiation of the Genelabs Phase II/III study was announced to the public in a May 10, 1994 press release (Attachment 11). In addition to these press releases and publications of study results, the existence of substantial clinical studies involving DHEA was reported in public documents published by investment analysts beginning no later than 1993 (Attachment 12). These studies were also publicly disclosed in documents filed by Genelabs with the Securities and Exchange Commission or issued to potential investors (Attachment 13).

FDA's issuance to Genelabs of an orphan drug product designation for the use of DHEA in the treatment of SLE on July 13, 1994 was also publicly disclosed (Attachment 14), as were FDA's designation of GL701 for expedited development under Subpart E (Attachment 13 (10-K for 1995)) and fast track review (Attachment 9). These publicly disclosed regulatory decisions also served to advise the public that DHEA was under clinical investigation as a new drug.

Furthermore, the results of both of Genelabs' Phase II/III and Phase III studies were publicly disclosed. The results of the Phase II/III study were disclosed in November 1997 at the American College of Rheumatology National Scientific Meeting (Attachment 7), and the results of the Phase III study were announced via press release on September 21, 1999 (Attachment 9). Subsequently, the data from this Phase III study were presented at the Eighth International Scientific Conference on Lymphocyte Activation on February 14, 2000 (Attachment 15).

Despite the fact that a large number of substantial clinical studies of DHEA were initiated and publicly disclosed beginning no later than 1988, some may attempt to rely upon the district court opinion in *Pharmanex, Inc.* v. *Shalala,* 35 F. Supp. 2d 1341 (D. Utah 1999) to argue that the GL701 formulation of DHEA as well as the DHEA formulations studied by Elan Pharmaceuticals, UCSD, and Stanford University are not the same "article" as the various DHEA products being marketed as dietary supplements, and that therefore the evidence of these prior investigations into DHEA does not exclude the products from the definition of "dietary supplement" under Section 201(ff)(3)(B)(ii) of the Act. First, Genelabs believes that the *Pharmanex* decision incorrectly interpreted Section 201(ff)(3)(B) of the Act and notes that this case is presently on appeal to the US. Court of Appeals for the 10th Circuit. Second, unlike in *Pharmanex*, which involved two allegedly well-characterized products, there are dozens of products being marketed as DHEA dietary supplements, with wide variations in the labeled amount of DHEA (*see, e.g.,* www.netrition.com/dhea_in_page.html, offering DHEA capsules ranging from 10mg - 100 mg) as well as the actual amount of DHEA versus the amount stated on the label (Attachment 16). Thus, the only logical method of regulating DHEA products is on an ingredient basis. Third, even assuming that the district court in *Pharmanex* correctly interpreted Section 201(ff)(B)(3)(i) of the Act, the court's analysis would not apply to Section 201(ff)(B)(3)(ii). Unlike the approved new drug considered in *Pharmanex*, investigational new drug formulations are subject to significant change prior to approval.

Interpreting Section 201(ff)(3)(B)(ii) as requiring a precise match between the investigational product and the formulation marketed as a dietary supplement would effectively render Section 201(ff)(3)(B)(ii) null and void.

D. DHEA was not marketed as a dietary supplement or a food prior to the date on which FDA authorized clinical investigations of DHEA as a new drug, or prior to the date on which these investigations were instituted and made public.

Prior to the passage of the DSHEA in October 1994, FDA interpreted the FFDCA as prohibiting the marketing of DHEA without prior approval of a new drug application. In the mid-1980's, FDA instituted a broad enforcement effort to prevent the marketing of DHEA as a "natural product" without an NDA. On July 9, 1984, FDA issued DLC-Rx Drug Study Bulletin # 265, which was followed by "Fraud Bulletin #5" on March 28, 1985. In the Fraud Bulletin, the Acting Chief of the Drugs and Biologics Fraud Branch authorized all FDA regional directors, district directors, and station chiefs to issue regulatory letters to all manufacturers and distributors of DHEA charging them with violating the FFDCA (Attachment 17). Numerous regulatory letters were then issued to DHEA manufacturers and distributors across the country, warning them that DHEA was a new drug that could not be legally marketed without an approved new drug application, and requiring them to cease manufacturing or distributing DHEA (Attachment 18). There were also a number of recalls of DHEA products (Attachment 19).

Genelabs discussed this regulatory history and its implications for the legal status of DHEA in a meeting with Agency representatives on February 4, 1997. In that meeting, the FDA representatives stated that products affected by the 1985 regulatory actions would not be considered food or food supplements, but that products marketed prior to DSHEA for which no drug claims, or no claims of any nature, were made might have been considered to be food products. They stated that it would be necessary to determine whether DHEA products were in distribution in the United States as food

products prior to public disclosure of any clinical trial of DHEA as a drug, and if so, the extent and nature of such distribution. The FDA representatives further informed Genelabs that proof of prior distribution could be based on a search of advertising, market surveys, and industrial orders.

In response to FDA's comments, Genelabs conducted an extensive research survey to determine whether there was a history of U.S. marketing of DHEA as a food prior to public disclosure of information from an IND involving DHEA. This survey, which was submitted to FDA on August 24, 1998 (Attachment 20) and discussed with Agency representatives during a March 31, 1999 meeting, provides substantial and credible evidence that DHEA was **not** sold as a food or food supplement from the time of the DHEA ban in 1985 until some time after the passage of the DSHEA in October 1994. Presumably, dietary supplement companies initiated DHEA sales after the passage of the DSHEA in reliance on the DSHEA's provisions that legalized the marketing of products claimed to be "dietary supplements" without prior FDA approval.

The results of the Genelabs survey thus also demonstrate that the marketing of DHEA as a dietary supplement began many years after the initiation and public disclosure of numerous clinical trials involving DHEA, such as the Elan Pharmaceuticals study (1988) and the UCSD studies. In addition, the survey provides convincing evidence that the marketing of DHEA as a dietary supplement began substantially later than the authorization of Genelabs' Phase II/III study in December 1993, and its initiation and public disclosure on May 10, 1994.

E. The Secretary has not issued a regulation finding that the marketing of DHEA as a dietary supplement would be lawful under the FFDCA.

The Secretary has not issued a regulation, after notice and comment, finding that the marketing of DHEA as a dietary supplement would be lawful under the FFDCA.

To summarize, substantial clinical trials involving DHEA as a new drug were authorized by FDA and initiated beginning no later than 1988. For more than 10 years, various studies of DHEA as an investigational drug have been disclosed to the general public, the investment community, and the scientific community in press reports, public securities filings, investment analysts' reports, scientific meetings and symposia, and peer-reviewed scientific journals. Moreover, there is no evidence to show that DHEA was legally marketed as a dietary supplement or a food prior to the authorization, initiation, and disclosure of these clinical investigations. Consequently, DHEA-containing products are excluded from the definition of a dietary supplement under Section 201(ff)(3)(B)(ii) of the Act.

## V. ALLOWING THE MARKETING OF DHEA AS A DIETARY SUPPLEMENT WOULD UNDERMINE THE STATUTORY SCHEME DESIGNED TO PROTECT THE PUBLIC HEALTH AND PROMOTE THE DEVELOPMENT OF NEW DRUGS

The 1994 enactment of the DSHEA altered the regulation of dietary supplement products. The drafters of DSHEA did not, however, intend to allow companies to circumvent the FFDCA's process of premarket review of new drugs, which is intended to protect the public health and prevent consumer fraud, merely by calling their products dietary supplements. *See* Senate Report No. 103-410, at 13 (1994). The provision of the DSHEA excluding articles approved as new drugs from the definition of dietary supplements (FFDCA § 201(ff)(3)(B)(i)), as well as the exclusion of products authorized for clinical study as drugs that were not marketed as dietary supplements or foods prior to the issuance and public disclosure of such authorization (FFDCA § 201(ff)(3)(B)(ii)), are intended to protect the integrity of the new drug approval scheme by preventing the marketing of new drugs without submission of the necessary safety and effectiveness data. Therefore, the exclusion of products containing DHEA from the definition of

"dietary supplement" is consistent with the purposes of the DSHEA and is in harmony with the overall regulatory scheme in the FFDCA.

In addition to requiring premarket review of safety and effectiveness for new drugs, the FFDCA provides a system of non-patent exclusivity incentives to promote the development of new drugs, in particular drugs for rare diseases or disorders. A developer of an approved new drug is entitled to five years of non-patent exclusivity, during which time no abbreviated new drug application which refers to such drug may be submitted. FFDCA §§ 505(j)(4)(D)(ii), 505(c)(3)(D)(ii). For products designated as "orphan drugs," *i.e.*, drugs intended for the treatment of diseases or conditions which affect fewer than 200,000 persons in the United States or for which there is no reasonable expectation of recouping the cost of developing and marketing the drug, the statute provides a special seven-year period of non-patent market exclusivity for the NDA holder. During the seven-year exclusivity period, no other person may submit an application for premarket approval of that drug for the same disease or condition. FFDCA §§ 526(a)(2), 527(a). In addition, FDA regulations provide a mechanism for expedited review of orphan drug products. 21 CFR Part 312, Subpart E. Also, patentable drugs may receive patent protection under Title 35 of the United States Code, and FDA and the United States Patent and Trademark Office have entered into an interagency Memorandum of Understanding providing procedures for the expedited review of patent applications for orphan drugs. *See* FDA Compliance Policy Guide No. 7155j.02 (May 1, 1984).

Furthermore, Section 506 of the Act authorizes FDA to designate a drug for "Fast Track" review if the drug is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for patients with the condition. FDA may take appropriate actions to facilitate the development and expedite the review of such a "Fast Track" drug (*see generally* Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review (September 1998)).

Genelabs has invested substantial resources to avail itself of these marketing incentives with respect to the development of DHEA for the treatment of SLE. Genelabs applied for and received IND 44,258 and instituted large-scale clinical investigations of the safety and effectiveness of DHEA for treating SLE, with the goal of submitting an NDA for treatment of SLE using DHEA. Genelabs also entered into an exclusive marketing agreement with Stanford University whereby Genelabs receives exclusive worldwide marketing and sublicensing rights to Stanford's DHEA patent and clinical results while Stanford receives milestone and royalty payments based on future clinical development goals and figures. In addition, Genelabs successfully applied to FDA for an orphan drug designation for DHEA for treatment of SLE, a rare, chronic disorder affecting approximately 150,000 individuals in the United States. FDA also designated DHEA for the treatment of SLE for expedited review under 21 CFR Part 312, Subpart E, and subsequently designated the product for "Fast Track" review. Finally, Genelabs has received a patent, U.S. Patent No. 5,567,696, for its method of treating SLE with DHEA to reduce the dosage of concomitant corticosteroids, which is currently the most common treatment for lupus.

Allowing DHEA to be marketed as a dietary supplement would undermine this complex scheme designed to protect the public health and promote development of new drugs, in particular new drug therapies for rare diseases and disorders. For patients, the integrity of the system of premarket drug approval to determine safety and effectiveness, as well as the continued strength of the system of incentives for investment in research and development of new drugs, is critical. Because DHEA is not a legitimate dietary supplement, as demonstrated in Part IV of this petition, allowing the continued marketing of DHEA as a dietary supplement will undermine this system designed to protect the public health and will create significant disincentives for future investment in the study and development of important new drugs, particularly drugs for "orphan" diseases such as SLE.

## VI. FDA SHOULD ACT PROMPTLY TO RESOLVE THE REGULATORY STATUS OF DHEA

For more than three years, Genelabs has been meeting and corresponding with FDA representatives to urge the Agency to reach a reasoned decision regarding the regulatory status of DHEA. After FDA representatives requested in February 1997 that Genelabs submit information to show that DHEA was not marketed as a dietary supplement or a food prior to clinical investigations into DHEA, Genelabs conducted extensive research that included database searches of relevant periodicals for DHEA advertisements, literature searches, and requesting information from dozens of dietary supplement manufacturers, distributors, and trade associations The results of this research, which were submitted to FDA on August 24, 1998 and discussed with Agency representatives during a March 31, 1999 meeting, provide substantial and credible evidence that DHEA was **not** sold as a dietary supplement from the time of the DHEA ban in 1985 until some time after the passage of the DSHEA in October 1994. Nevertheless, despite Genelabs' diligent efforts to respond to FDA's requests for additional information, and despite the Agency's acknowledgment of the seriousness and legitimacy of Genelabs' concerns, the Agency has not yet taken action to resolve this issue.

Genelabs urges FDA to act promptly, because of the effect FDA's decision (or absence of one) may have on the ability to make GL701 available to patients with SLE if the NDA is approved by FDA in 2001. As noted, Genelabs plans to begin submission of a "rolling" NDA for DHEA in the first half of this year, with the complete submission expected before the end of the year. At present, Genelabs is primarily a research and development company with only limited sales and distribution capabilities.

It would be a tragedy for patients suffering from SLE if the availability of GL701 were prevented or delayed due to the continued uncertainty regarding the sale of DHEA

as a "dietary supplement." SLE is a life-long, devastating autoimmune disease that primarily affects women, many of whom experience the initial onset of the disease in their late teens and early twenties. SLE can result in serious and life-threatening organ damage, involving inflammation of the brain tissue and kidney failure. Current treatment is primarily limited to inflammation suppression, most commonly through chronic use of steroids such as prednisone. Long-term use of steroids has many serious adverse consequences, including premature osteoporosis, atherosclerosis, and diabetes. Nevertheless, it has been 40 years since a new therapy has been introduced to treat this disease. The availability of GL701 as a prescription drug would enable patients suffering from SLE to reduce their reliance on steroids, which would represent a major improvement in the treatment of this disease. Indeed, by designating GL701 as a "Fast Track" product, FDA recognized that this new therapy would meet an important unmet medical need for SLE patients.

DHEA products sold as "dietary supplements" would not represent an acceptable substitute for an FDA-approved prescription medication. As has been documented, DHEA products currently being marketed as "dietary supplements" are not manufactured under adequate quality controls. Many of these products show significant discrepancies between the amount of DHEA contained in the product versus the amount stated on the label (*see* Attachment 16). Consequently, patients cannot rely on these products to deliver an appropriate and consistent dose of DHEA. Moreover, dietary supplement products are not accompanied by the crucial FDA-approved labeling that allows physicians and patients to administer and use the drug in a safe and effective manner. The entire system of premarket clinical investigation of new drugs and postmarketing surveillance for unanticipated adverse effects is geared toward the generation of adequate information about the benefits and risks associated with taking a drug product. But DHEA products marketed as "dietary supplements" would not (and indeed could not legally) provide such information to physicians and patients. Section 201(ff)(3)(B)(ii) of

the Act is intended to balance the rights of health food consumers against the needs of patients In this case, Genelabs submits that the statute **compels** the prohibition of the marketing of the drug DHEA as a "dietary supplement."

No matter what the outcome, FDA should act promptly to avoid further delay in resolving this issue and to prevent any unnecessary disruption in the availability of GL701 for patients suffering from SLE.

## VII. BENEFITS OF THE PROPOSED PROCESS

The process proposed in this petition is the appropriate approach for determining whether DHEA is excluded from the definition of "dietary supplement." The proposed process provides due notice to all interested persons and enables them to participate in the decisionmaking process by coming forward with relevant information. The process shifts the burden of proof from Genelabs, which has been placed in the inequitable position of having to prove a negative (*i.e.*, establishing that DHEA was **not** marketed as a dietary supplement or food prior to the initiation and disclosure of substantial clinical trials), to those who are in the best position to produce the records and data necessary to resolve the relevant questions. It defines the evidence needed to establish that DHEA was previously marketed as a food or food supplement. Genelabs' specific proposal is based on established FDA practices from the new drug "grandfather" clause regulations (21 C.F.R. § 314.200(e)(2)) and the new dietary ingredient regulations (21 C.F.R. Part 190), but focuses on the key questions for determining prior marketing under Section 201(ff)(3)(B)(ii) of the Act -- what the product was sold for and for how long. Moreover, the proposed process provides FDA an orderly mechanism for compiling the administrative record needed to support a legal determination that DHEA is excluded from the definition of "dietary supplement," if that is the outcome of such a process.

Finally, the proposed process will advise all interested parties of the time frames in which this determination will be made. If no substantial and credible evidence is submitted within the 60-day comment period purporting to show that DHEA is not excluded from the definition of "dietary supplement," there is no reason for FDA to delay in issuing a final ruling. In such a case, Genelabs' *prima facie* showing will not have been overcome, and the administrative record will compel a determination that DHEA-containing products may not be marketed as "dietary supplements." If substantial and credible evidence to rebut Genelabs' position is submitted, the time frames established in this proposal provide FDA ample time to weigh all the evidence and issue a reasoned decision.

## VIII. CONCLUSION

The evidence described in Part IV of this petition establishes a *prima facie* case that DHEA is excluded from the definition of "dietary supplement" under Section 201(ff)(3)(B)(ii) of the Act. To allow all interested parties to submit evidence on the legal status of DHEA, FDA should publish a *Federal Register* notice in the form of Attachment 1 within 30 days of receipt of this proposal. If, upon the close of the comment period, FDA has not received substantial and credible evidence demonstrating that the requirements of the FFDCA Section 201(ff)(3)(B)(ii) have not been established with respect to DHEA, FDA should immediately issue a determination that DHEA may not be marketed as a dietary supplement. If FDA has received such evidence, FDA should weigh the evidence against the evidence presented in the present submission by Genelabs, as well as all other information received in response to the *Federal Register* notice, and publish a reasoned determination in the *Federal Register* whether DHEA is excluded from the definition of dietary supplement under FFDCA Section 201(ff)(3)(B)(ii).

## IX. ENVIRONMENTAL IMPACT

Pursuant to 21 C.F.R. § 25.30(a), the issuance of procedural or administrative regulations and guidelines, including procedures for submission of applications for product development, testing and investigational use, and approval, is categorically exempt from the requirement of an environmental assessment or an environmental impact statement. Also, the establishment by regulation of labeling requirements for marketing articles is categorically exempt if there will be no increase in the existing levels of use or change in the intended uses of the product or its substitutes. 21 CFR § 25.30(k). The relief requested by this petition would, at most, result in (1) the issuance of an administrative regulation or guideline affecting product development, testing, investigational use, and approval, and/or (2) the establishment by regulation of labeling requirements for marketing articles which would not result in any increase in the existing levels of use or change in the intended uses of the product or its substitutes. To petitioner's knowledge, no extraordinary circumstances exist. Thus, no environmental assessment is required.

## X. ECONOMIC IMPACT

Information on the economic impact of this petition will be submitted if requested by the Commissioner.

## XI. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which petitioner relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

Marc Gurwith, M.D.
Vice President of Drug Development and
Chief Medical Officer

## ATTACHMENTS

**Attachment 1** (Proposed Form of Notice)

**Attachment 2** (Press Reports of 1988 Elan IND and published study results)

**Attachment 3** (Yen Memorandum dated January 31, 1997 regarding UCSD studies and published study results)

**Attachment 4** (FDA letter dated January 6, 1994 regarding IND 44,258)

**Attachment 5** (Nov. 11, 1993 Press Release)

**Attachment 6** (Documentation of Phase III Trial Enrollment)

**Attachment 7** (April 25, 1997 and September 30, 1997 press releases)

**Attachment 8** (FDA letter dated March 31, 1999)

**Attachment 9** (September 21, 1999 press release)

**Attachment 10** (1994 and 1995 published results of Genelabs Phase II studies)

**Attachment 11** (May 10, 1994 Press Release)

**Attachment 12** (Investment analysts' publications)

**Attachment 13** (Excerpts from SEC filings and securities prospectus)

**Attachment 14** (Orange Book listing for DHEA)

**Attachment 15** (February 14, 2000 press release)

**Attachment 16** (Parasrampuria et al., "Caveat Emptor – Dehydroepiandrosterone (DHEA) Dietary Supplement Products: Quality Control Discrepancies")

**Attachment 17** (Fraud Bulletin #5)

**Attachment 18** (Regulatory letters)

**Attachment 19** (Recall announcements)

**Attachment 20** (Genelabs Survey Regarding Prior Marketing of DHEA)